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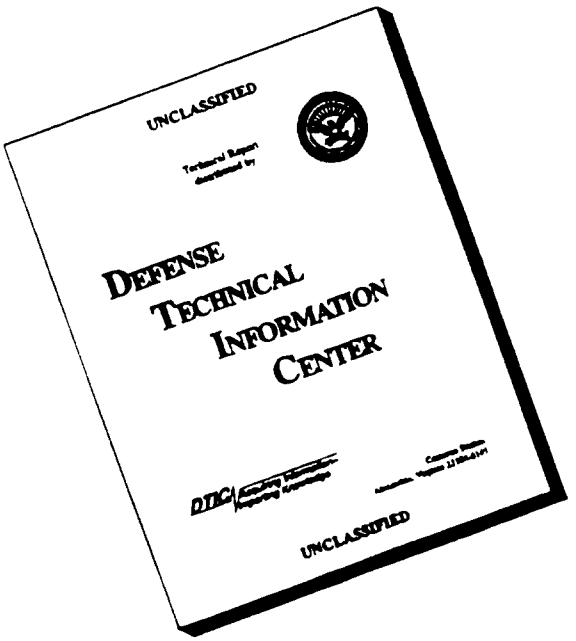

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13. ABSTRACT *(Maximum 200*

There is a growing need for interactive computational tools for medical education and research. The most exciting paradigm for interactive education is simulation. Fluid Mod is a simulation based computational tool developed in the late sixties and early seventies at the RAND corporation. Fluid Mod is designed around solving problems in equilibrium solution chemistry. It functions by minimizing the free energy of complex chemical systems. Fluid Mod used simulation to present students with cases in need of diagnosis and therapy. Even though it was useful, Fluid Mod had an archaic interface and could not easily be extended to serve as a research tool. In this Phase I effort, Critical Concepts ported Fluid Mod to a modern Windows, object oriented interface. This development will provide students with a useful computational tool for learning. More important still, it serves as a platform for development of a better, more sophisticated modeling tool for biochemical and medical research.

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Richard W Sammel Jr
Principal Investigator's Signature

Oct 13, 1996
Date

Contents

Introduction and Overview of Completed Effort

In this Phase I effort, Critical Concepts ported Fluid Mod to C++ for Windows. A derivative of the research tool Chemist, Fluid Mod was an educational tool for medical students that implemented a reduced-complexity model of blood and of the human body. Like Chemist, Fluid Mod had an obsolete, clumsy and limited user interface. Porting Fluid Mod produced a user-friendly training program for students of medical fluid therapy. It shows that a complex scientific engine can be made easy to use.

This document serves as the final report for the Phase I effort. We have intentionally omitted all material on the relationship of Phase I to the proposed Phase II work, because we have already submitted a detailed Phase II contract proposal under separate cover. Please see that submission for a description of the work proposed for Phase II. Portions of that proposal, relevant to how Fluid Mod works, have been repeated here.

The Phase I work, to be discussed in detail below, was successful in most respects. As was our goal, the program itself has been completed and is ready for beta testing. In previous communications, we have described difficulties: the matrix formulation was obscure, the units and scaling in the original version were poorly documented, and in many cases had to be deduced from context. At the end of six months, the program (version 0.9) was mostly functional, but still had significant glaring errors and several omissions. These problems have been resolved. The present version is designated 1.0 Beta, and this version number implies that it is ready for beta testing (our original goal for the end of Phase I).

Because of the scientific difficulties that cropped up while performing the work, we have focused on the scientific core of the program and have not yet completed a minor goal: that of producing a printed \manual. However, the program comes with an automated installation procedure that will work on Windows 3.1, Windows 95, and Windows NT, and comes with complete online instructions, right in the program, in a hypertext format. Thus, it remains completely usable even without a printed manual. We acknowledge that omission, and will rectify it forthwith. The other eleven goals of our Phase I effort have been met.

Phase I Work Description

The objective of Phase I was to port Fluid Mod to C++ for Windows. The core of this work is complete. In the course of porting Fluid Mod, we learned a great deal about the equilibrium solution system developed at the RAND corporation, and obtained a clear understanding of the strengths and limitations of this approach to biochemical simulation.
Specific Subtasks

1. Compile a working Fortran version for use in verification of the new system
2. Develop a requirement specification for program outputs and interface
3. Develop a content testing protocol, for later validation and verification
4. Perform code analysis with goals of subtask isolation
5. Perform direct syntactical translation
6. Extract translated code into new functional subunits
7. Design and build a new interface and "front end" for Fluid Mod
8. Assemble the final translation by coupling the interface to the translated engine
9. Validate and verify the new program against the results of the old program
10. Develop external documentation (online help, manual, technical report)
11. Outline potential educational strategies for use of the program
12. Develop a requirement specification for the Phase II program.

With the exception of item 10, we have completed all of these objectives as `desired`.

This experience puts us in an excellent position to develop a system of much larger and more sophisticated scope, that will provide users with a superset of the combined capabilities of Fluid Mod and its big brother, Chemist.

The original version of Fluid Mod consisted of several components:

(1) A system to load a sparse matrix from disk

(2) A system to solve chemical equilibrium problems based on numerical handling of this sparse matrix

(3) A kinetic model of the kidney

(4) Code to adjust the volumes of various compartments to adjust for age and size

(5) A disparate collection of code to perform various accessory tasks, such as converting mole fractions into simulated laboratory results and exam findings.

(6) A system to handle cases by reading a computer card-oriented file with capability of encoding up to 20 cases.

The task of porting this system to Windows required extricating all of these capabilities from the original FORTRAN, documenting the code, and reproducing it in a modern object oriented platform. Inherent in this is a strict separation of user interface code from scientific model code, that is essential for porting and maintaining the code. It also required developing a new interface that could make Fluid Mod easy to use.

Translated elements of Fluid Mod code.

(1) Sparse Matrix (Model) Loading.

The first objective of our port was to eliminate the sparse matrix formulation in the original Fluid Mod. Use of sparse matrices was sensible when computer memory was measured in kilobytes. However, in this day and age, the entry-level personal computer comes with 16 Megabytes of RAM and there is no longer any reason to use the more memory efficient but less readable sparse matrix approach. Accordingly, when we loaded the matrix into memory, we elected to create a fully populated matrix. Large amounts of code for indexing had to be removed from the system, and this turned out to be a major headache. However, once completed, the resulting code is clearer, easier to read, and better to verify and maintain. So the trade was more than equitable.

(2) Chemical Equilibrium Solution.

Elimination of the sparse matrix handling from the system memory also required major efforts to clean up the solution engine. This also turned out to be a challenge, but we currently have a properly object oriented C++ language solution system that produces the exact same results as the original version. The new version has clearer logic, better internal documentation, and therefore will be useful for performing a port of some of the internals of Chemist, which has a better and more sophisticated (but still sparse-matrix bound) solution engine.

(3) Renal Model

Apart from the Lagrange Multiplier/Simplex method in the equilibrium solution engine, the most sophisticated part of Fluid Mod was a renal model. The renal model assumed GFR based on size, age, and hydration status of the patient, and then modeled transfer of a variety of plasma solutes to and from the tubular fluid. This renal model was an example of a rather sophisticated kinetic process that was needed in addition to the equilibrium problem solver itself. There was no actual framework within Fluid Mod to systematically handle such processes, but we built a generic rate process model, of which the kidney was a descendant, to handle the transfer of fluids for systems that could not be handled as in continuous equilibrium. This will serve as a forerunner of the plans for incorporation of generic rate processes into the Phase II development. Given this development the port of renal effects to the new system will be straightforward.

(4) Normalization

In Fluid Mod, various straightforward nomograms were used to describe the variation in compartment size due to age. These routines were translated with fairly little change.

(5) Calculation of user inputs and outputs:

Fluid Mod's code for interacting with the user, presenting data, and the like was a real nightmare. The code was widely dispersed, poorly documented, and needed centralization. It is in this area that we have the most continuing problems. We have developed a generic way to handle infused fluids and oral fluids. We have developed new code for systematically reporting patient results. We have organized laboratory value calculation in a single, straightforward object. However, some of the calculations are still incorrect, and for this reason the system is not yet usable even though the internal code is nearly complete.

(6) Case handling in Fluid Mod was via a single large text file that had room for 20 cases, where individual numbers in various locations had meanings that depended critically on their alignment. Loading a case meant searching through the case file and pulling out those numbers that corresponded to the particular case. We have eliminated this approach to case handling. The replacement approach simply puts all information about a particular case into a single file, as a sequence of text instructions written in a scripting language developed for this work. This gives a simple way to add, subtract, or change cases

without great difficulty. A handful of other FORTRAN-specific limitations to case file handling have also been removed.

(7) Changes to incorporation of fluids into the modeled human body.

Fluid Mod incorporated fluids into the body by putting some of each administered component into each compartment. The amount to infuse was roughly the same for each, despite the fact that compartments were dissimilar in size and composition. We substituted a linear extrapolation technique to improve the solution and lessen the likelihood of getting a solution failure.

Methods from equilibrium thermodynamics

To explain the RAND corporation solution system, we offer a few words of introduction prior to describing the solution method itself. The second law of thermodynamics states that equilibrium corresponds to a system state at which entropy is a maximum. Entropy maximization works only for closed systems with constant energy and volume; for systems at constant temperature and pressure, equilibrium is the state that minimizes Gibbs free energy[1].

The chemical equilibrium calculations performed in Chemist, which will be carried over into Cell Simulator, are a direct application of this last form of the second law. Let us briefly discuss how this is done.

A particular model has a variety of chemical reactants -- let x_j denote the number of moles of each component. Then it turns out that we can characterize the total free energy of the system by the sum of the free energy of each of the constituents. Letting μ_j denote the free energy per mole of the jth constituent, the total free energy of that constituent becomes $x_j\mu_j$. Hence we can calculate the total free energy as:

$$G = \sum_j x_j \mu_j$$

This equation represents G as a function of the set of mole numbers and of their respective molar free energies. Fortunately, the molar free energy of a constituent is a fairly simple function of the mole number itself:

$$\mu_j = \mu_{oj} + \log(\frac{x_j}{S})$$

Here, S represents the sum of all the moles of all the components in the system, and μ_{0j} represents the standard free energy of that particular chemical -- i.e. just a constant. So the above equations give a simple way to calculate the total free energy of the entire system.

Obviously this is not the whole story. The sum of all the partial Gibbs free energy terms should drive the chemical reaction toward minimum values for every component -- but this violates the obvious premise that there are actually reactants present. So this equation is meaningless without additional information about the system for which it is evaluated.

What we have left out (thus far) is the conservation of mass: the total mass of reactants is a constant. The thermodynamic calculations must minimize free energy *subject to this constraint*. Let us explore an example of a constraint. When CO_2 binds to OH^- to form HCO_3^-, the mole number of CO_2 and OH^- decrease, while the mole number of HCO_3^- increases[2]. There are obvious constraints here: the total mass of each atom is obviously conserved, but the mass of particular products are not.

The character and identity of a particular problem come not from the thermodynamic second law, but rather from the amount of the chemical constituents and from the reactions they can undergo. This means that the science of a thermodynamic model is all contained in the set of constraints that characterizes the

---

[1] The Gibbs free energy is defined as E - TS + PV, where E is energy, T is temperature, S is entropy, P is pressure, and V is volume. In mathematical terms this is a Legendre transformation (cf. Callen) with respect to entropy and volume, which merely changes variables so that one can examine a system whose temperature and pressure are fixed by contact with an outside reservoir, rather than a system whose volume and energy are fixed by containment in a closed box.

[2] Contrary to popular opinion, this appears to be the reaction catalyzed by carbonic anhydrase. This is known on the basis of solution kinetics: no reaction can occur faster than the rate of diffusional matching of substrate to enzyme. But the rate of liberation of CO_2 by carbonic anhydrase exceeds the diffusional rate limit if one assumes the enzyme substrate to be H_2CO_3. The only way to overcome such limits is to pick a substrate that exists at a higher concentration, and the only CO_2 source present in high enough concentration is HCO_3^-. The activity of the reverse reaction is known on the basis of detailed balance arguments.

model. And the problem of making a nice interface to the thermodynamics means finding a convenient way to write down all of the reactions, and to figure out how to translate this into a set of constraints. The set of mathematical constraints can be written down as a set of equations that limit the relationship between the mole numbers:

$$b_i = \sum_j x_j a_{ij}$$

Here, b_i and a_{ij} are constants. This set of equations may initially appear obscure, but in fact is rather simple to understand. For example, one equation for the red cell system comes from the conservation of mass. We can track the total mass of CO_2 and related species using a simple equation:
CO_2 (total) = CO_2 (dissolved) + CO_3^{--} + HCO_3^- + H_2CO_3.
This equation is just a mass conservation equation. To represent this equation in the formalism above, we set b_i as the total number of moles of CO_2, and the values of a_{ij} equal to the coefficients 1, 1, 1, and 1 for the four j's that correspond to the mole numbers of dissolved CO_2, carbonate, bicarbonate, and carbonic acid, respectively. Since other constituents (e.g. Na^+, H_2O, etc) do not contribute anything to the mass balance for carbon dioxide, the aij is given values of zero for all other values of j.
One can systematically write such equations for every constraint the system must handle. Of course, one one goal of this proposal is to let the computer automate this otherwise cumbersome process.
Given a set of equations of constraint and the standard free energies of the chemical constituents, the system is ready to be solved. This is the function of the code contained within Chemist and Fluid Mod. The problem is a three step process: differentiate the Gibbs free energy equation with respect to each mole number, and set the results equal to zero (to find the stable state). This gives an equation for each mole number. Second, use the method of undetermined multipliers[3] is used to incorporate the set of constraints (a_{ij} and b_j). Third, once these are incorporated, the Simplex[4] method is used to search the multidimensional solution space to find the set of mole numbers that minimize the overall Gibbs free energy function.

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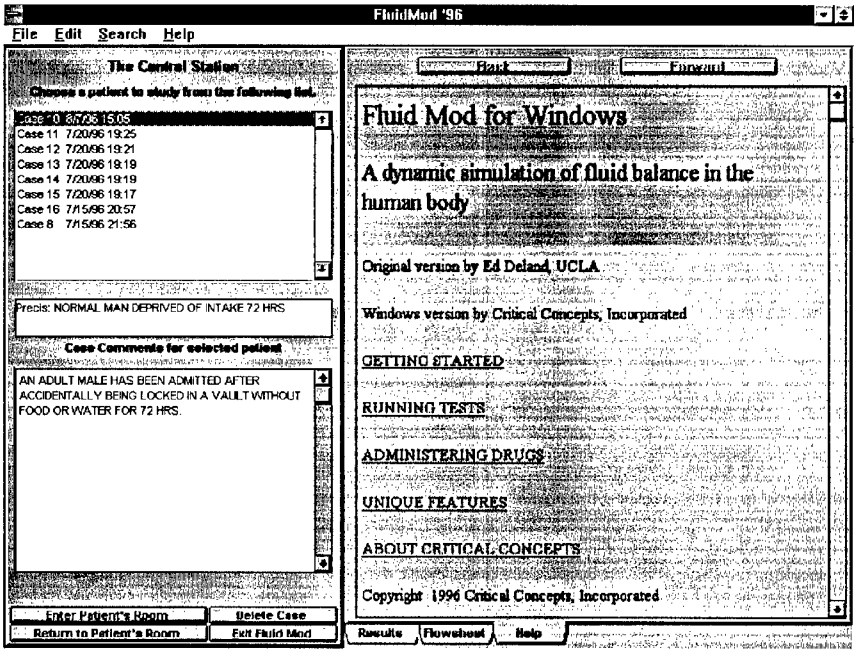
[3] The method of undetermined multipliers, originally due to Lagrange, has a long history of use in solving optimization problems in the presence of constraints. The idea is simple: to solve a pair of equations with two unknowns, you eliminate one of the variables. In order to subtract two equations and have a term fall out, multiply the first equation by a coefficient and then subtract. Lagrange pointed out that you don't have to say what the value of the coefficient is until the end of the solution process, and that this can simplify incorporating equations of constraint. Clear expositions of Lagrange's undetermined multipliers are found in a variety of sources (cf. Reif, Page, Wilf).

[4] The Simplex method, developed by Dantzig at the RAND corporation in the 1950's and 1960's is a method for figuring out maximum and minimum values of some function of a large set of variables (see White, Wilf). The approach is based on an orderly method for searching vertices on a manifold that represents possible solutions.

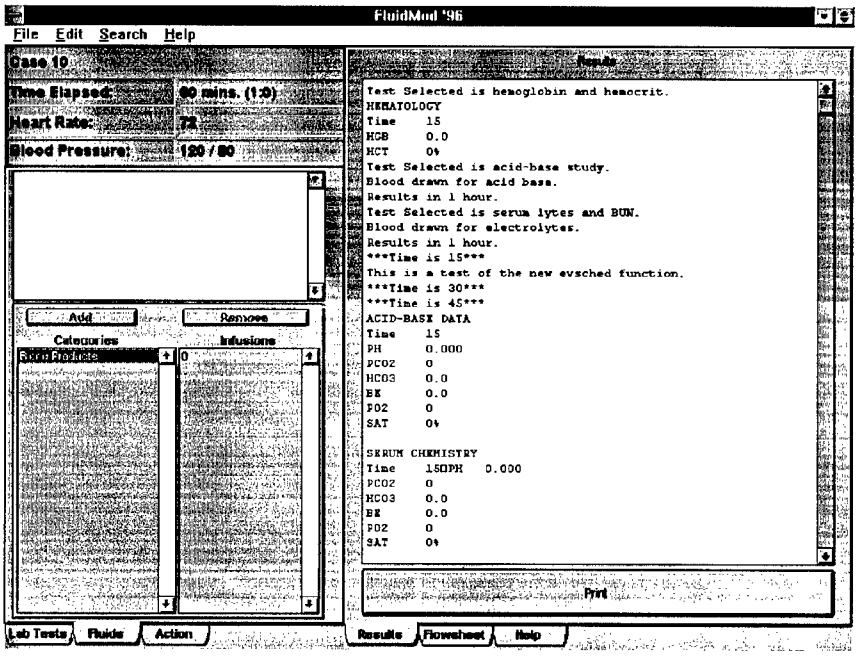
The Fluid Mod Interface

The objective of Fluid Mod is to present the student with a simulated patient, and to let the student carry out interventions and see what happens over time. When the student loads Fluid Mod, he or she is presented with a list of patients from which to choose. The appearance of the central station is shown below. There is a list of patients on the left, and a help window visible on the right.



Fluid Mod has a tabbed interface. The left side of the screen shows interventions that users select. The right side of the screen shows the current state of the patient, with or without any other documentary information the student might want to explore. To switch between pages, the user merely clicks on the tab at the bottom of the page.

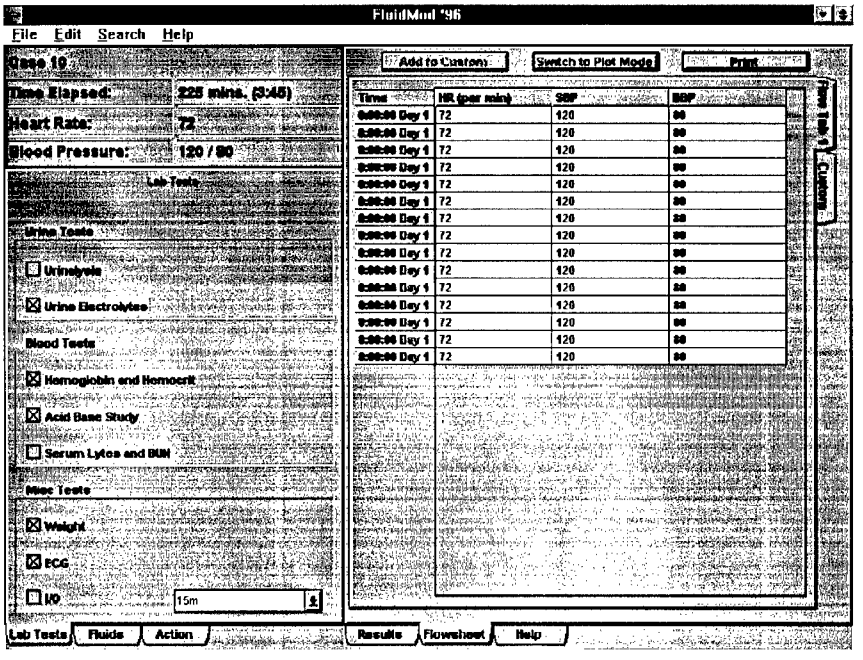
When the program is running, students can select drugs or fluids from an infusion list. The fluids are kept in two categories: IV fluids and PO fluids. Users merely select specific fluids from this list. Once selected, users set the rate and volume (for IV fluids) or the dose frequency and volume (for PO fluids). The upper left hand corner of the screen shows the time and vital signs of the patient.

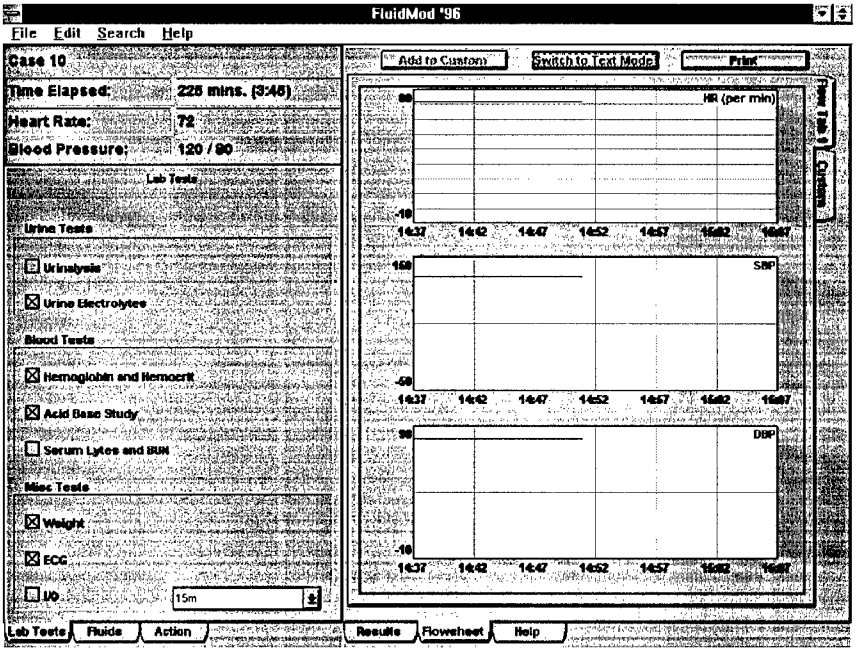


The right hand side of the page tells the user what events have transpired as well as giving results from any lab tests that are performed.

The Fluid Mod Flowsheet

The flowsheet (shown on the right, in each case) is another clipboard full of data. In the beta version, there are six different tabs along the right hand side, showing time course of changes of various types of data. The data can be seen in tabular (top) or graphical (bottom) form.





Persisting Problems with Fluid Mod for Windows

Major problems with Fluid Mod for Windows fall in 3 groups:

(1) We anticipated producing a paper manual. This has not yet been completed. The relative simplicity of the user interface and the richness of the online help system should permit the manual to be fairly brief, so we expect that this manual will become available shortly.

(2) The solution engine (the system that solves the Gibbs Free Energy Minimization problem) runs too slowly. We believe that it should be possible to speed this up by a factor of two, and this will be done during Phase II.

(3) The system currently fails when executing some cases under some circumstnces. We are continuing to work with Dr. DeLand, beyond the end of the Phase I period, to eliminate these glitches.

(4) As expected, this version of Fluid Mod has not yet been tested in practice. We anticipate educational trials at UCLA as part of Dr. DeLand's teaching this December. Regardless of whether a Phase II contract is awarded, we plan to go ahead with this field testing.

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Appendix

We have included a copy of a CD entitled Fluid-Mod version 1.0. This CD contains an installable version of the software, and can run on a Windows 3.1, Windows 3.11, Windows for Workgroups 3.11, Windows 95, Windows NT 3.51, or Windows NT 4.0 computer. The computer should have a 486 or better microprocessor, and should have 8 MB or more of RAM.

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